POSTHER

Burden of herpes zoster and postherpetic neuralgia among people ≥ 50 years old in France

EPI-ZOSTER-020 BOD FR (201926)

Protocol V2

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

CNIL	French data privacy council (*Commission Nationale de l'Informatique et des Libertés*)
CNOM	National Council of Physicians (*Conseil National de l'Ordre des Médecins*)
CCP	French ethic committee (*Comité de Protection des Personnes*)
DMP	Data Management Plan
DRESS	Department for Evaluation and statistics of the French Health Ministry (*Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques)*
EQ-5D 5L	Health-related quality of life questionnaire
GPs	General Practitioners
HZ	Herpes Zoster
PHN	PostHerpetic Neuralgia
SAP	Statistical Analysis Plan
VHZ	Varicella Zoster Virus
ZBPI	Zoster Brief Pain Inventory (ZBPI)

KEY PERSONNEL

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SIGNATURE

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French Steering committee	Date & signature: NOV 03, 2014
French Steering commitee	Date & signature: Oct. 28, 2014
Laboratoire GSK	Date & signature: 28/10/2014
Laboratoire GSK	Date & signature: 23. 10. 2014

PPD

SYNOPSIS

TITLE Burden of herpes zoster and postherpetic neuralgia among people ≥ 50 years old in France: the POSTHER Study

RATIONAL AND BACKGROUND

Herpes zoster (HZ) is a painful disease resulting from the reactivation of the latent varicella zoster virus from dorsal root or cranial nerve ganglia. The annual incidence of HZ was estimated to 3.8‰ in France with a linear increase with age, and a lifetime risk of HZ to 26.5%.

Some people develop complications after an initial acute episode of HZ, such as encephalitis, peripheral nerve palsies, myelitis, herpes ophthalmicus and postherpetic neuralgia (PHN), the most frequent complication. PHN remains long after the HZ lesions have healed, and often persists for months or years. PHN was estimated to occur in 8% to 32% of people with HZ.

The burden of HZ and PHN is not well characterized in France. A prospective cohort of incident cases of HZ, diagnosed by community first line practitioners concerned by HZ diagnosis, represents a suitable approach to describe the burden of herpes zoster and postherpetic neuralgia among people ≥ 50 years old in France.

RESEARCH QUESTIONS AND OBJECTIVES

Research question: To assess the burden of HZ and PHN among people ≥ 50 years old in France, in terms of healthcare resources used, medical direct and indirect costs, as well as pain severity and impact on quality of life.

Primary objective

- To evaluate HZ-related and PHN-related direct medical costs and indirect costs during a 9-month period (overall, by gender and age-classes).

Secondary objectives

- To describe HZ and PHN pain severity during a 9-month period (overall, by gender and age-classes),
- To evaluate impact of HZ and PHN on the quality of life of patients during a 9-month period (overall, by gender and age-classes).

STUDY DESIGN

An observational, prospective cohort study of patients ≥ 50 years old with a HZ diagnosis, carried out by a national random sample of community first line practitioners concerned by HZ diagnosis: general practitioners (GPs), dermatologists and ophthalmologists.

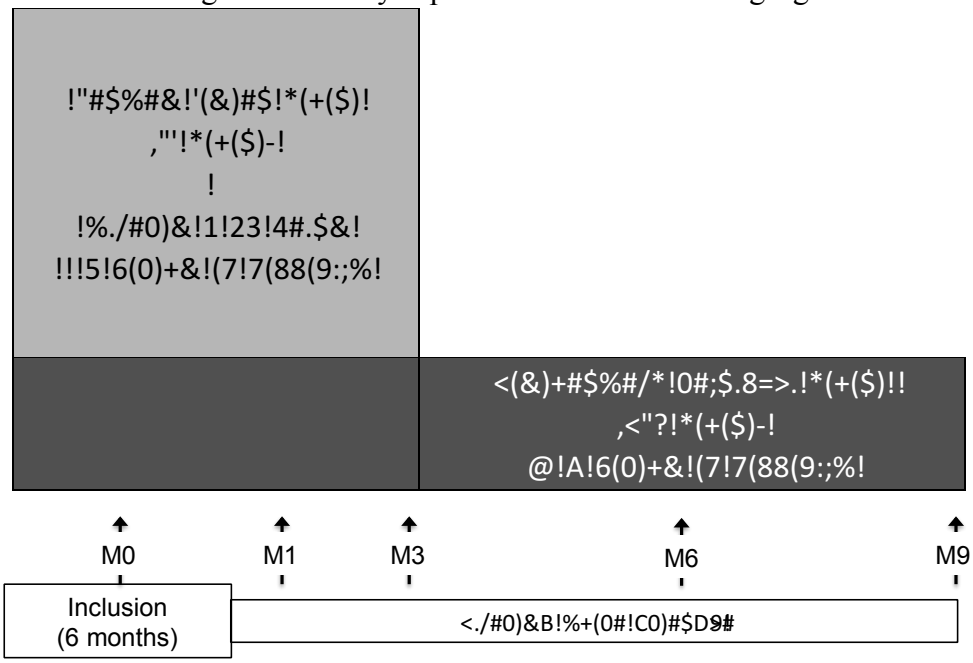
Inclusion

- HZ cohort: All patients ≥ 50 years old with a HZ diagnosis (as the primary diagnosis and without history of previous HZ) during approximately 6 months inclusion period will be included in the HZ cohort, until total study target is achieved (competitive inclusion),
- PHN cohort: All patients of the HZ cohort presenting PHN (defined as ZBPI pain ≥3) 3 months after HZ rash onset symptoms will be included secondarily in the PHN cohort.

Follow-up

- **HZ cohort:** Patients of the HZ cohort will be followed-up for 3 months using phone interviews with a nurse 1 and 3 months after HZ rash onset (M1 ± 3 days, M3 ± 1 week).
- **PHN cohort**: Patients of the PHN cohort will be followed-up for another 6 months using phone interviews with a nurse 6 and 9 months after HZ rash onset (M6 ± 1 week, M9 ± 1 week).

The overall design of the study is presented in the following figure:



POPULATION

Study carried out by a random sample of community first line practitioners concerned by HZ diagnosis: GPs, dermatologists and ophthalmologists.

HZ cohort inclusion-exclusion criteria

- Patient with a first visit for a diagnosis of HZ and who attend the clinic within two week of the HZ start of symptoms (defined as unilateral pain accompanied by a unilateral rash without alternative diagnosis),
- Patient ≥ 50 years old without history of previous HZ,
- Patient who agree to participate and signed informed consent,
- Patient able to understand the study, to complete self-administered questionnaires (alone or with the help of a relative) and to answer to phone interviews.

PHN cohort inclusion-exclusion criterion

- Patient of the HZ cohort presenting PHN 3 months after onset of the HZ rash onset (defined as the presence of HZ-associated severe "worst" pain: pain ≥ 3 from ZBPI item "worst pain")

VARIABLES

Index date: date of HZ rash onset.

PHN: "worst pain" item ≥ 3 from the Zoster Brief Pain Inventory (ZBPI) questionnaire ≥ 3 months after index date.

Outcomes:

- Direct medical cost: medical visits, emergency room (≤ 24h), hospitalisation (≥ 24h), drugs prescribed, procedures performed or prescribed in relation with HZ or PHN.
- Indirect cost: patient sick leave.
- HZ and PHN severity: three categories for last 24h worst pain from ZBPI questionnaire: mild pain (0<pain<3), moderate pain (3 ≤ pain < 7) and severe pain (7 ≤ pain).
- Quality of life and utilities: EQ-5D 5L heath state.

Patients' and disease characteristics at inclusion.

DATA COLLECTION	**Inclusion** **From participating physicians** ▪ Inclusion-exclusion criteria, ▪ Date of visit, ▪ Patient's characteristics (gender, date of birth, current occupational status), ▪ HZ characteristics (date of rash onset, prodromal symptoms, rash localization, complications, contributing factors, immunosuppressant drugs), ▪ Drugs used and prescribed for HZ with dosage and duration, ▪ Sick leave prescription and duration, ▪ Patient referred to a specialist or hospital and reason(s). **Signed patient informed consent** with contact details to send booklets and to realize phone interviews. **Patient self-administered questionnaire at inclusion** ▪ ZBPI questionnaire, ▪ EQ-5D 5L health state. **Follow-up** **Patient phone interview at: M1, M3, M6 in case of PHN declared at M3 and M9 in case of PHN declared at M6.** **Phone interview will be realized** with the help of a patient booklet given to the patient to report week by week HZ and PHN-related healthcare resources used during the past three months (between M1 and M3, M3 and M6, M6 and M9): ▪ Date of the interview , or reason if it can't be done, ▪ Drug used with dosage and number of boxes, ▪ Sick leave prescription and duration, ▪ Number of GP visits, specialist visits, emergency room (≤ 24h) and reasons, ▪ Hospitalization (≥ 24h), reason and duration. ▪ ZBPI questionnaire, ▪ EQ-5D 5L health state.
STUDY SIZE	• 250 cases of HZ and 40 cases of PHN expected (hypothesis of 16% of PHN at M3). • Approximately 170 GPs, 20 dermatologists and 20 ophthalmologists with the hypotheses of a mean of 1 patient ≥ 50 years old with HZ diagnosis per GPs and 2 per specialist over a 6-month inclusion period. • Assuming 2/3 of active participation, approximately 210 GPs, 30 dermatologists and 30 ophthalmologists will be recruited.
STATISTICAL ANALYSIS	• Flowchart of physician recruitment and cohort inclusion (HZ and PHN). • **Primary objective**: description of healthcare resources used with

valorisation to estimate direct medical and indirect cost per episode (overall, by gender and age-classes) from a payer and societal perspective:
  - For the HZ cohort during the study period (M0, M1 and M3);
  - For the PHN cohort during the study period (M0, M1, M3, M6 and M9).
- **HZ and PHN severity**: Description using ZBPI questionnaire with three categories for last 24h worst pain: mild pain (0<pain<3), moderate pain (3 ≤ pain < 7) and severe pain (7 ≤ pain).
  - For the HZ cohort during the study period (M0, M1 and M3);
  - For the PHN cohort during the study period (M0, M1, M3, M6 and M9).
- **Quality of life and utilities**: description of EQ-5D 5L and associated utility score:
  - For the HZ cohort during the study period (M0, M1 and M3);
  - For the PHN cohort during the study period (M0, M1, M3, M6 and M9).
- The EQ-5D 5L health state will be used to estimate utility and to estimate loss in quality of life associated with HZ and PHN. The EQ-5D 5L will be converted into a single summary index showing the utility function over time. The comparison of these utility scores with existing reference value set derived for EQ-5D in France will provide the average loss in quality of life (so-called QALY weights) associated with HZ and PHN.
- Statistical correlations between HZ and PHN severity (three categories defined above) and cost on the one hand and severity and utility scores on the other hand will be derived.
- Description of the patients' and disease characteristics at inclusion.

PROJECTED MILESTONES	Protocol and CRF	Oct. 2014
	Administrative phase	Oct. 2014 – Feb 2015
	Physician recruitment	Mar-Apr 2015
	Inclusion period (6 months)	Apr-Sept 2015
	End of follow-up (9 months)	Jun 2016
	Data management and analysis	Jul 2016-Sept 2016
	Scientific Board	Oct 2016
	First Version of study report	Nov 2016

AMENDMENTS AND UPDATE

Number	Date	Section of study protocol	Amendment or update	Reason

1 RATIONAL AND BACKGROUND

Herpes zoster (HZ) is a painfull disease resulting from the reactivation of the varicella zoster virus (VHZ). Upon primary infection VHZ becomes latent in the dorsal root or cranial nerve ganglia. Following a variable period of latency time, VHZ can reactivate to produce an infectious virus. This virus can travel to the skin and re-infect it causing a vesicular rash accompanied by acute pain in the region of the affected dermatome (*Arvin 2000, Kennedy 2002, Dworkin 2007*).

The incidence of HZ in the United States and Western Europe varies from 1.4 to 4.8 per 1 000 person-years with 20% to 30% of people affected by HZ in their lifetime (*MacDonald 2000, Chidiac 2001, Insing 2005, Dworkin 2007, Yawn 2007, Gonzales 2010, Mick 2010, Pinchinat 2013*). Older age and immunodeficiency states (cancer, autoimmune disease, HIV infection, immunosuppressive drug…) are associated with an increased risk of HZ (*Pope 2004, Insinga 2005, Sharvadze 2006*).

In France, the General Practitioners' (GPs) sentinel electronic surveillance network estimated the lifetime risk of HZ to 26.5% and the annual incidence of HZ to 3,8‰ between 2005 and 2008, with a linear increase with age (*Gonzales 2010*). In a retrospective study using medical files of a random sample of GPs, dermatologists, neurologists and departments of pain management the 2005 annual incidence of HZ was estimated to 9.0‰ of patients aged 50 years and above (*Mick 2010*), which is concordant with the results of older population of the GPs sentinel network study.

Some people who experience an initial acute episode of HZ develop complications (*Dworkin 2007*). These include encephalitis, peripheral nerve palsies (both rare complications), myelitis, herpes ophthalmicus and postherpetic neuralgia (PHN), the most frequent complication. PHN is a debilitating condition in which neuropathic pain remains long after the HZ lesions have healed, and often persists for months or years. The classic definition is chronic pain persisting 3 months after rash onset. As with other HZ complications, the elderly and patients with immunodeficiency are at a higher risk for the development of PHN (*Insinga 2005*).

PHN is estimated to occur in 8% to 32% of people with HZ overall (*Di Luzio 1999, Helgason 2000, Oxman 2005, Scott 2006, Insinga 2007, Gauthie, 2009; Mick 2010, Bouhassira 2012*), depending on the PHN definition, time since the onset of the acute phase, age of the study population and probably the study methods. In the French retrospective study cited above, the proportion of patients aged 50 years and above presenting PHN at 3 and 6 months was 32.1% and 17.6% respectively (*Mick 2010*); while a large prospective study with French GPs estimated the prevalence of PHN among patients aged over 50 years to 11.6%, 8.5%, 7.4% and 6.0% at 3, 6, 9 and 12 months respectively, with higher prevalence in patients ≥ 70 years old (*Bouhassira 2012*).

Several studies have shown that HZ has a negative impact on quality of life and this negative impact was more important for patients with PHN (*Johnson 2010*). In England, HZ would be responsible for a lost 2000 quality adjusted life years (QALYS) and 87% of it in relation with PHN (*Insinga 2007*). The cost of the disease was studied in many countries (*Edmunds 2001, Kennedy 2002, Pope 2004, Yawn 2007, White, 2009*). The 2005 annual cost of HZ management and PHN in France was estimated to about 170 millions Euros of which 36% were covered by the national health insurance (*Mick, 2010*).

The burden of HZ and PHN is not well characterized in France. A prospective cohort of incident cases of HZ, diagnosed by community first line practitioners concerned by HZ diagnosis,

represents a suitable approach to describe the burden of HZ and PHN among people ≥ 50 years old in France.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective is to evaluate HZ-related and PHN-related direct medical costs and indirect costs during a 9-month period (overall, by gender and age-classes).

2.2 SECONDARY OBJECTIVES

Secondary objectives are:

- To describe HZ and PHN pain severity during a 9-month period (overall, by gender and ageclasses),
- To evaluate impact of HZ and PHN on the quality of life of patients during a 9-month period (overall, by gender and age-classes).

3 ENDPOINTS

The primary endpoint is HZ-related and PHN-related direct medical costs and indirect costs, estimated with the valorisation of the HZ and PHN healthcare resources used (medical visits, emergency room (≤ 24h), hospitalisation (≥ 24h), drugs prescribed, procedures performed or prescribed in relation with HZ or PHN, as well as patient sick leave).

Secondary endpoints are:

- **HZ and PHN severity** using three categories for last 24h worst pain from ZBPI questionnaire: mild pain (0<pain<3), moderate pain (3 ≤ pain < 7) and severe pain (7 ≤ pain). - **Quality of life and utilities** using EQ-5D 5L.

The index date is defined as the date of HZ rash onset.

PHN is defined as "worst pain" item ≥ 3 from the Zoster Brief Pain Inventory (ZBPI) questionnaire ≥ 3 months after index date.

4 STUDY DESIGN

An observational, prospective cohort study of patients ≥ 50 years old with a HZ diagnosis, carried out by a national random sample of community first line practitioners concerned by HZ diagnosis: general practitioners (GPs), dermatologists and ophthalmologists.

Inclusion

All patients ≥ 50 years old with a HZ diagnosis (as the primary diagnoses and no earlier case of HZ) during approximately 6 months inclusion period will be included in the **HZ cohort**, until total study target is achieved (competitive inclusion).

All patients of the HZ cohort presenting PHN 3 months after HZ rash onset symptoms will be included secondarily in the **PHN cohort**.

Follow-up

- **HZ cohort:** Patients of the HZ cohort will be followed-up for 3 months using phone interviews with a nurse 1 and 3 months after HZ rash onset (M1 ± 3 days, M3 ± 1 week).
- **PHN cohort:** Patients of the PHN cohort will be followed-up for another 6 months using phone interviews with a nurse 6 and 9 months after HZ rash onset (M6 ± 1 week, M9 ± 1 week).
- A postal mail or email will be sent 8-12 days before the phone interview with the ZBPI and EQ-5D 5L for the interview.

The list of procedures is presented in table 1 and the overall design of the study is presented in the following figure 1: Table 1: list of procedures

	HZ COHORT			**PHN COHORT**	
	Inclusion	M1 ± 3 days	M3 ± 5 week	M6 ± 1 week	M9 ± 1 week
Initiation activities that will be managed by the site					
Aggregated demographic data	X				
Signed patient agreement	X				
Eligibility criteria	X				
Medical history	X				
Clinical Diagnosis of HZ **Procedure performed or prescribed**	X				
HZ characteristics and co-morbidity **HZ severity**	X				
Healthcare resources prescribed **Direct and indirect cost**	X				
Patient booklet **Report week by week HZ-related healthcare resources used between Inclusion and M1**	X				
ZBPI Self-administered questionnaire	X				
EQ-5D 5L Health State **Selfadministered questionnaire**	X				
Follow up activities that will be managed during the phone interviews					
ZBPI questionnaire		X	X	X	X
EQ-5D 5L Health State		X	X	X	X
Healthcare resources used **Direct and indirect cost**		X	X	X	X

Sent reminder to patient for phone interview **8-12 days before phone date**		X	X	X	X
Sent the patient booklet Report week by week HZ-related healthcare resources used during the next three months			X	X	X

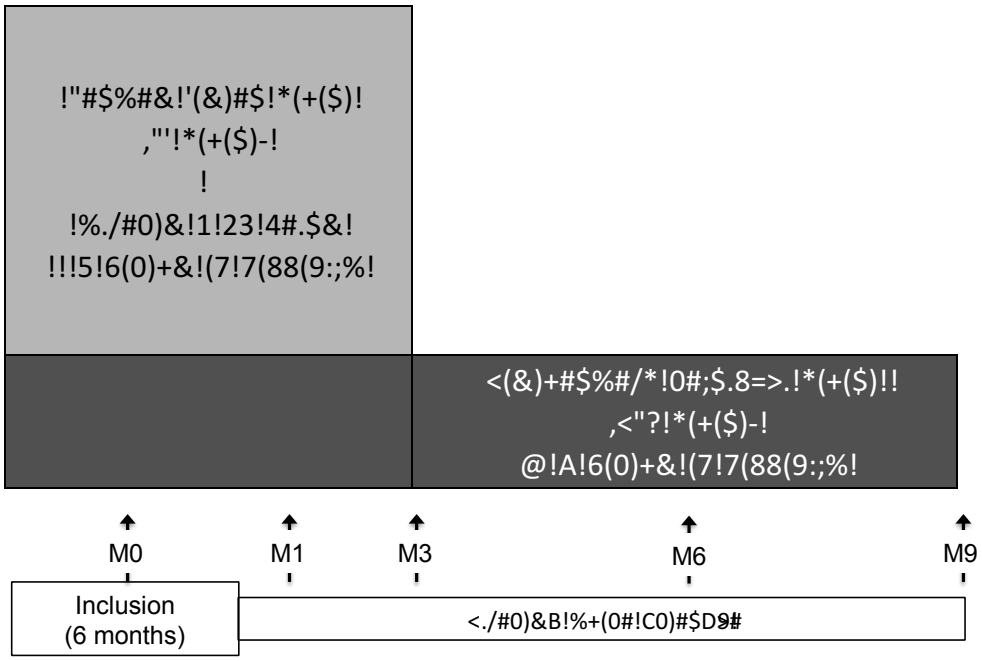


Figure 1: study design

5 STUDY POPULATION

5.1 PHYSICIANS

The study will be carried out by a random sample of approximately 210 community first line practitioners concerned by HZ diagnosis: 210 GPs, 30 dermatologists and 30 ophthalmologists with the hypothesis that 2/3 of them will be active (≥ 1 patient included), i.e. about 170 GPs, 20 dermatologists and 20 ophthalmologists (cf. 7.2 Physician sample size).

5.2 PATIENTS

The study has been designed to include 250 patients ≥ 50 years old with a first visit for a diagnosis of HZ during a 6-month inclusion period (HZ cohort) and 40 expected PHN 3 months after HZ rash onset (cf. 7.1 Patient sample size).

5.2.1 HZ cohort inclusion and exclusion criteria

To be included in the HZ cohort, patients have to fulfill all the following criteria:

- Patient with a first visit for a diagnosis of HZ and who attend the clinic within two week of the HZ start of symptoms (defined as unilateral pain accompanied by a unilateral rash without alternative diagnosis),
- Without history of previous HZ,
- ≥ 50 years old,
- Who agree to participate and signed informed consent,
- Able to understand the study, to complete self-administered questionnaires (alone or with the help of a relative) and to answer phone interviews.

5.2.2 PHN cohort inclusion and exclusion criterion

All Patients of the HZ cohort presenting PHN 3 months after onset of the HZ rash onset will be included in the PHN cohort. PHN will be defined as the presence of HZ-associated severe pains: ≥ 3 of the ZBPI item "worst pain".

6 DATA COLLECTION

6.1 SIGNED PATIENT AGREEMENT

All patients included in the HZ cohort will have to sign a patient informed consent, including contact details to send booklets and to realize phone interviews: − First name, surname, postal and email address, phone number(s), − Preferred time to be contacted for a phone interview.

All patients included in the HZ cohort will receive a patient booklet at inclusion, to report weekby-week HZ-related healthcare resources used during the next three months. The following patient booklet (for the next three month period) will be sent by courier.

6.2 HZ COHORT

For all patients included in the HZ cohort, physicians will have to complete a medical questionnaire with the following information:

- Inclusion-exclusion criteria
- Date of visit,
- Gender, date of birth, current occupational status,
- HZ characteristics: date of HZ rash onset, prodromal symptoms, rash localization, pain evaluation (ZBPI questionnaire), complications (cutaneous, neurological, ocular, HZ oticus, visceral, other),
- Pre-existing contributing factors:
  - Emotional problem, stress, depression,
  - Alcoholism
  - Tabagism
  - Diabetes, renal failure or dialysis, liver disease,
  - Hepatitis C under active therapy in the 12 months before HZ diagnosis,
  - HIV infection with low CD4 count (≤ 350 CD4/µl) or history of opportunistic disease or other AIDS related conditions any time before HZ diagnosis,

- Solid malignancy: active chemotherapy or widespread radiation therapy, or statement of metastatic or active disease in the 6 months before the diagnosis of HZ,
- Blood malignancy: active chemotherapy or widespread radiation therapy, or statement of metastatic or active disease in the 6 months before the diagnosis of HZ,
- Solid organ transplantation in the 12 months before HZ diagnosis or longer but continues on anti rejection treatment.
- Hematopoetic cell/ bone marrow transplantation in the 12 months before HZ diagnosis or longer but continues on anti rejection treatment.
- Autoimmune disease active and under therapy: both a confirmed diagnosis of the condition and immunosuppressive therapy (5mg/d or more of oral corticosteroids or other immunosuppressive therapy) required in the 12 months before HZ diagnosis (e.g. Rhumatoid arthritis, systemic Lupus Erythematosus, inflammatory Bowel Disease, Ankylosing Spondylitis, Psoriasis and other to be specified),
- Immunosuppressive medications: Oral or parenteral corticosteroids, Cytostatics/ Chemotherapy treatment, Monoclonal and polyclonal antibodies, post transplantation anti rejection treatment / Drugs acting on immunophilins (Cyclosporin, tacrolimus, sirolimus), or other drugs to be specified.
- Other drugs,

- Drug used and prescribed (name, dosage and number of boxes) for HZ,
- Patient sick leave prescription and duration,
- Patient referred to a specialist or hospital and reason(s).

6.3 PATIENT SELF-ADMINISTERED QUESTIONNAIRE AT INCLUSION

All patients included in the HZ cohort will have to complete the 2 following self-administered questionnaires:

- ZBPI questionnaire,
- EQ-5D 5L health state.

6.4 PATIENT PHONE INTERVIEW DURING THE FOLLOW-UP:

A patient phone interview will be organized with a nurse by the Coordinating Center at M1 and M3 for all patients included in the HZ cohort, and at M6 and M9 for all patients included in the PHN cohort. The following information will be completed during the phone interview, using a patient booklet (to report weekly HZ-related healthcare resources used during the last three months):

- Date of interview or the reason why the interview could not be done: patient agreement withdrawal, lost to follow-up, death and other to be specified.
- Healthcare resources in relation with HZ or PHN since the last contact (inclusion or followup phone interview):
  - Drug used with dosage and number of boxes,
  - Sick leave prescription and duration
  - Number of GP visits, specialist visits, emergency room (≤ 24h) and reasons,
  - Hospitalization (≥ 24h), reason and duration. − ZBPI questionnaire, − EQ-

5D 5L health state.

A postal mail or email will be sent 8-12 days before the planned interview to propose a date and time for the interview with the opportunity to plan another appointment, and to provide selfadministered questionnaires (ZBPI and EQ-5D 5L) for the interview, as well as the patient booklet for the next three months.

A patient will be declared "lost to follow-up" if he cannot be reached after 5 call attempts distributed over one week, and if he does not ask for another appointment for the interview. In such a case, the physician will be contacted to try to document the reason.

7 STUDY SIZE

7.1 PATIENT SAMPLE SIZE

The study has been designed to include 250 cases of HZ with 40 cases of PHN expected (hypothesis of 16% of PHN at M3). For quantitative variables, such as costs and utilities, the precision will be a function of the variability of the variable. Table 1 shows that a sample of 250 cases, the precision will be between ± 3.1% and 24.8 % for a standard deviation between 1/4 and 2 times the mean, and 40 cases a precision of the mean of between ± 7.7% and 62.0 % for a deviation standard between 1/4 and 2 time the mean.

Table 1: *Precision of a 95% confidence interval for a continuous variable, taking into account the standard deviation and sample size, according to the normal distribution for the mean (n ≥ 30)**

Sample size (n)	**Standard Deviation (SD as % of the mean)**					
	1/4	**2/4**	**3/4**	**1**	**1,5**	**2**
250	3,1%	6,2%	9,3%	12,4%	18,6%	24,8%
40	7,7%	15,5%	23,2%	31,0%	46,5%	62,0%

* ±1.96 * SD/√n, with SD the Standard deviation and n the sample size.

*standard deviation and sample size, according to the normal distribution for the mean (n ≥ 30)**

Sample Size (n)	standard deviation (SD)				
	25	50	500	2000	4000

Table 2 : *Precision of a 95% confidence interval for a continuous variable, taking into account the*

250	3,10 €			6,20 €
	61,98 €			247,92 €
	495,85 €			
40	7,75 €			15,50 €
	154,95 €			
	619,81 €		1 239,61 €	

* ±1.96 * SD/√n, with SD the Standard deviation and n the sample size.

7.2 PHYSICIAN SAMPLE SIZE

In the study of the General Practitioners' (GPs) sentinel electronic surveillance network, the average yearly number of cases reported by each GP was 3.31 (95% CI 2.82–3.80) (*Gonzales 2010*). For this study, we assume that GPs and specialists will include at least mean number of 1 and 2 cases respectively, for a 6-month inclusion period. With this hypothesis, a random sample 170 GPs, 20 dermatologists and 20 ophthalmologists could include 250 cases of HZ.

In such studies, some participating physicians are not active, especially with scarce patients such as HZ cases. Assuming 2/3 of active participation, 210 GPs, 30 dermatologists and 30 ophthalmologists will be recruited.

8 DATA-MANAGEMENT

A Data Management Plan (DMP) will define the database characteristics (item names and formats, dataset structure), as well as edit checks to ensure validity of database with a focus on missing, implausible or inconsistent data. The DMP will be approved prior to initiating data entry.

A double data entry will be performed for the medical questionnaires, while phone interviews will use a direct single data entry during the interview. Data entry, database management and edit checks will be performed continuously during the study.

9 DATA ANALYSIS

Statistical analysis will be performed using SAS® software (SAS Institute, last version, North Carolina, USA). A Statistical Analysis Plan (SAP) will be developed and validated by the Scientific Committee before the analysis. The following statistical analysis will be performed.

9.1 STUDY POPULATION

A flowchart will summarize physician recruitment (contacted, refusing to participate and reasons, agreeing to participate, active), patient inclusion (in HZ and PHN cohorts) and withdrawn from the study and reasons.

9.2 PHYSICIANS

Physician characteristics (gender, age) will be compared to the National statistics of GPs, dermatologists and ophthalmologists from the Department for Evaluation and statistics of the French Health Ministry (DRESS: Direction de la recherche, des études, de l'évaluation et des statistiques).

9.3 PATIENTS INCLUDED

Patient and disease characteristics at inclusion will be described for patients included in the HZ cohort and in the PHN cohort.

9.4 OUTCOME

- **Primary objective**: Healthcare resources used will be described with estimation of the direct medical and indirect cost per episode (overall, by gender and age-classes) from a payer and societal perspective:
  - For the HZ cohort during the study period (M0, M1 and M3);

  - For the PHN cohort during the study period (M0, M1, M3, M6 and M9).
- **HZ and PHN severity** will be described with three categories for last 24h worst pain: mild pain (0<pain<3), moderate pain (3 ≤ pain < 7) and severe pain (7 ≤ pain):
  - For the HZ cohort during the study period (M0, M1 and M3);
  - For the PHN cohort during the study period (M0, M1, M3, M6 and M9).
- **Quality of life and utilities** will be described using EQ-5D 5L and derived utility score:
  - For the HZ cohort during the study period (M0, M1 and M3);
  - For the PHN cohort during the study period (M0, M1, M3, M6 and M9).
- Statistical correlations will be estimated between HZ and PHN severity (three categories defined above) and cost on the one hand, and severity and utility scores on the other hand will be derived.

9.5 STATISTICAL METHODS

- Qualitative variables (dichotomous or categorical) will be described in terms of number and frequency, as well 95% confidence interval (95%CI) for main variables, estimated using normal approximation distribution.
- Quantitative variables will be described in terms of mean, standard deviation, geometrical mean, median, first and third quartiles, minimum and maximum as well 95% confidence interval (95%CI) for main variables.
- The EQ-5D 5L health state will be used to estimate utility and to estimate loss in quality of life associated with HZ and PHN. The EQ-5D 5L health states will be converted into a single summary index showing the utility function over time. The comparison of these utility scores with existing reference value set derived for EQ-5D in France will provide the average loss in quality of life (so-called QALY weights) associated with HZ and PHN

10 QUALITY CONTROL

A quality control will be performed for a random sample of 10% of active physicians with:

- On-site, face-to-face with participating physician to check adherence to the protocol, that all eligible patients were included, and collected data (major clinically-relevant data),
- Verification of consistency between entered data and physician-completed inclusion paper CRF for corresponding patients.

11 LIMITATIONS OF THE RESEARCH METHODS

Selection bias:

The study will be carried out with a national random sample of community first line practitioners concerned by HZ diagnosis, in order to identify a representative sample of patients with HZ first visit. However, active physicians are not necessarily representative for the others. The representativeness of active physicians will be evaluated by comparing their general characteristics to the national data from the Ministry of Health (*Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques / DREES*).

Moreover, the study does not concern primary severe cases that should be hospitalized without a first visit with a first line practitioner, or patients yet hospitalized for another cause. However, this situation has been considered to concern very few patients.

In order to avoid a patient selection bias by physician, all patients ≥ 50 years old with a first visit for HZ will be included in the study. Patients lost to follow-up are the main source of attrition bias in cohort studies. In this study, the risk of loss of follow-up has been minimized using direct patient contact with phone interview.

Information bias:

Data collected by physicians at inclusion are usual in HZ diagnosis and no suspected information bias has been identified, nor frequent missing value risk. In order to avoid missing values during follow-up phone interviews with patients, self-administered questionnaires (ZBPI and EQ-5D 5L) will be sent by mail before the phone interview, and an patient booklet, to report week by week HZ-related healthcare resources used, given at inclusion and then sent by mail for the M1, M6 and M9 visit.

12 PROTECTION OF HUMAN SUBJECTS

12.1.1 Ethic Committee (CPP)

According to the French law (n°2004-806 of the 9/08/2004, article 88,), this study is an observational research, without specific drug evaluation, and with only small risks and constraints for the patients (follow-up visits and phone interview). The protocol will be submitted to a French Ethics Committee (*Comité de Protection des Personnes / CPP*).

12.1.2 National Council of Physicians (CNOM)

According to the French Public Health Code (article L.4113-6), the study protocol and the research agreements for investigators and members of the Scientific Committee will be submitted to the National Council of Physicians (*Conseil National de l'Ordre des Médecins / CNOM*).

12.1.3 Data privacy (CNIL)

The use of patient ID number and initial is justified in order to link patient documents (inclusion medical questionnaire and phone interview during follow-up), as well as edit checks and quality control on site. The use of nominative data (title, first names, surname, phone number, home and email address,) is justified to contact the patient for phone interviews during the follow-up. In order to keep medical confidentiality, two independent networks and servers will be used, one for nominative data and the other for medical information. An information letter related to data collection and data privacy will be given to the patient prior to entering the study and a patient agreement will be dated and signed by the patient.

According to the chapter IX of French Data Privacy Law (n° 78-17 of the 6/01/1978, n° 94-548 of the 1/07/1994 et n°2004-801 of the 6/08/2004) the protocol and CRF will be submitted first of all to the French independent review board for data privacy in health research (*Comité Consultatif sur le Traitement de l'Information en matière de Recherche sur la Santé / CCTIRS*) and then to the French Data Privacy Commission (*Commission National de l'Informatique et des Libertés / CNIL*) for authorization.

13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

It is an observational epidemiologic study without specific drug evaluation. According to the article R.5121.170 of Public Health Code, physicians, dentists, or midwives having noticed an adverse event suspected to be related to a medicinal product or to a product referred to in article R.121-150, whether they are or not the prescriber, have to make the immediate declaration to the Regional Centre of Pharmacovigilance (CRPV).

14 PLAN FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study methods and results will be discussed with the scientific meetings and submitted for presentation in scientific meetings and publication in international scientific journals. The report and publications will be used to support market authorizations of a HZ vaccination to prevent PHN.

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